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Suzuki–Miyaura Cross-Coupling of *N*-Acylpyrroles and Pyrazoles: Planar, Electronically Activated Amides in Catalytic N–C Cleavage

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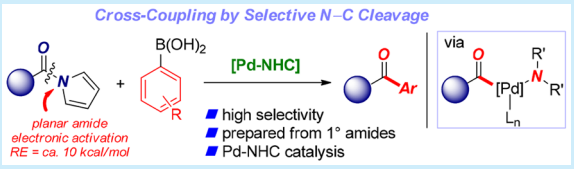
Supporting Information

ABSTRACT: The formation of C–C bonds from amides by catalytic activation of the amide bond has been thus far possible by steric distortion. Herein, we report the first example of a general Pd-catalyzed Suzuki–Miyaura cross-coupling of planar amides enabled by the combination of (i) electronic-activation of the amide nitrogen in *N*-acylpyrroles and pyrazoles and (ii) the use of a versatile Pd-NHC catalysis platform. The origin and selectivity of forming acylmetals, including the role of twist, are discussed.



The development of efficient methods for coupling of amides by transition-metal-catalyzed N–C bond cleavage has become an important goal in organic synthesis.[1,2] With this bond forming manifold, typically considered inert amide bonds can be harnessed into generic acyl-metal reactivity pathways.[3] Given that amides represent ubiquitous synthons in biologically active compounds and common intermediates in organic synthesis,[4] the discovery of new catalytic reactivity by amide N–C cleavage undoubtedly holds a significant potential in various fields of chemistry.[5,6]

While methods that induce N–C bond activation[7] in sterically distorted amides[8] have now been well-established,[9] catalytic processes that enable C–C bond formation from planar amides are absent (Figure 1A). Recently, Maiti and co-workers reported an excellent method for Ni-catalyzed step-down reduction of amides to aromatic hydrocarbons using *N*-acylpyrazoles as the reaction partners (Figure 1B).[10] In the extensive mechanistic studies, it was elegantly shown that N–Ni-coordination at the 2-position of the pyrazole ring is critical for high reactivity; unfortunately, synthetically valuable *N*-acylpyrroles[11] were found unreactive in this process. The method constitutes a rare example of activating planar amide bonds in Ni catalysis.[12]

Herein, we report a Pd-catalyzed activation of N–C amide bonds in planar amides enabled by electronic activation of the amide N atom (Figure 1C). Cross-coupling of planar amides is significantly more challenging than that of distorted amides as distortion disrupts amidic resonance more effectively than electronic destabilization.[1b] The following features of our study are noteworthy: (1) we demonstrate the high reactivity of both *N*-acylpyrroles and *N*-acylpyrazoles, resulting in an operationally simple, catalytic synthesis of biaryl ketones from *N*-acylpyrroles as Weinreb amide equivalents, without resorting to a two-step protocol via tetrahedral intermediates (Figure 2).[11] (2) Since *N*-acylpyrroles can be readily prepared from primary benzamides (the Paal–Knorr pyrrole synthesis),[13] our method offers a rapid entry to metal-catalyzed coupling of unactivated primary amides.

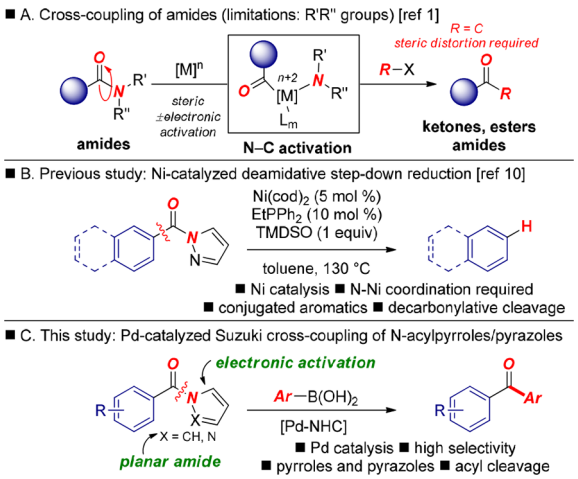


Figure 1. (a) Metal-catalyzed activation of amides and derivatives. (b) Ni-catalyzed reduction of *N*-acylpyrazoles. (c) Coupling of *N*-acylpyrroles and pyrazoles.

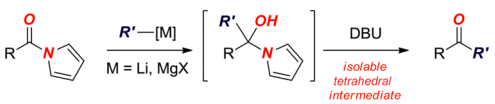


Figure 2. Previous state-of-the-art: ketone synthesis from *N*-acylpyrroles using organolithiums or Grignard reagents.[11]

(3) We demonstrate the beneficial effect of Pd-NHC (NHC = *N*-heterocyclic carbene) catalysis[14] over Pd-phosphines in the activation of inert amide N–C bonds,[9r,t] which may have implications for the design and optimization of amide cross-coupling manifolds. (4) Mechanistic studies provide insight into the origin and selectivity of forming acylmetals from *N*-

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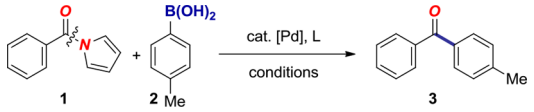
acylpyrroles,[1−3] including the role of twist on the reactivity. Collectively, our study opens an avenue for generating acyl-metal intermediates from planar, electronically activated amides for a range of catalytic coupling reactions via acyl and decarbonylative pathways.

Recently, our laboratory introduced new protocols for cross-coupling of sterically activated amides by ground-state resonance destabilization.[9h−m] In this context, we examined the reactivity of sterically distorted *N*-acyl-2,5-dimethylpyrrole (<5% yield,[9h] τ = 39.7°; χ_N = 8.4°,[15] Winkler−Dunitz distortion parameters). We questioned whether electronic activation of nitrogen through delocalization of N_{lp} into the π-electron system of the pyrrole ring[16] may be sufficient to selectively insert palladium into the amide N−C bond in the absence of coordination or steric distortion, resulting in a general process.

After very extensive optimization, we found that Pd-NHC catalysis is indeed capable of promoting the desired reaction [(IPr)Pd(cinnamyl)Cl, 6 mol %, 4-Tol-B(OH)$_2$, 2.0 equiv, K_2CO_3, 3.0 equiv, THF, 110 °C]. Selected optimization results are summarized in Table 1. Of particular note, Pd-PR_3 systems

Table 1. Optimization of *N*-Acylpyrrole Cross-Coupling[a]



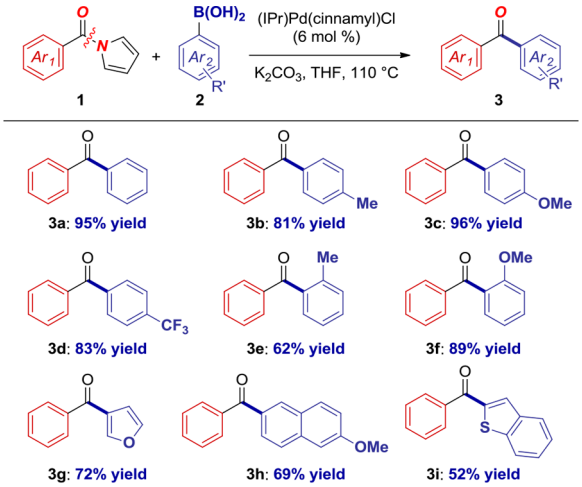
entry	catalyst	ligand	base	solvent	yield (%)[b]
1	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	THF	<2
2	$Pd_2(dba)_3$	PCy_3HBF_4	Na_2CO_3	dioxane	<2
3	$Pd(OAc)_2$	PPh_3	K_2CO_3	THF	<2
4	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	<2
5	$Pd(OAc)_2$	PPh_3	K_2CO_3	NMP	<2
6	$Pd(OAc)_2$	$PnBu_3$	K_2CO_3	THF	<2
7	$Pd(OAc)_2$	IPrHCl	K_2CO_3	THF	<2
8	(IPr)Pd(allyl)Cl		K_2CO_3	THF	82
9	(SIPr)Pd(cinnamyl)Cl		K_2CO_3	THF	57
10	(IPr)Pd(cinnamyl)Cl		K_2CO_3	THF	92
11	(IPr)Pd(cinnamyl)Cl		K_2CO_3	dioxane	<2
12	(IPr)Pd(cinnamyl)Cl		K_2CO_3	toluene	<2
13	(IPr)Pd(cinnamyl)Cl		K_3PO_4	THF	<2
14	(IPr)Pd(cinnamyl)Cl		KF	THF	<2
15	(IPr)Pd(cinnamyl)Cl		KOH	THF	<2
16	(IPr)Pd(cinnamyl)Cl		NaO*t*Bu	THF	<2
17[c]	(IPr)Pd(cinnamyl)Cl		K_2CO_3	THF	56

[a]Conditions: amide (1.0 equiv), R−B(OH)$_2$ (2.0 equiv), catalyst (6 mol %), base (3.0 equiv), solvent (0.50 M), 110 °C, 15 h. Entries 1−6: [Pd] (3 mol %), ligand (6 mol %). [b]GC/^{1}H NMR yields. [c][Pd] (3 mol %).

were found ineffective as catalysts for amide N−C cross-coupling (entries 1−6). We hypothesize that strong σ-donation of the NHC ligand in facilitating oxidative addition is critical for the N−C coupling reactivity. Evaluation of different Pd-NHC catalysts revealed (IPr)Pd(cinnamyl)Cl to be optimal (entries 7−10). At present, 110 °C is required for the coupling. The choice of base and solvent had a dramatic effect on the reaction efficiency (entries 10−16). Other bases (K_3PO_4, KF, KOH, NaO-*t*Bu) and solvents (dioxane, toluene) provided inferior results compared to K_2CO_3/THF.[14]

Having identified the optimal conditions, we next evaluated the scope of the reaction with respect to the boronic acid component (Scheme 1). As shown, these conditions are compatible with

Scheme 1. Boronic Acid Scope in the Pd-NHC-Catalyzed Cross-Coupling of *N*-Acylpyrroles[a,b]

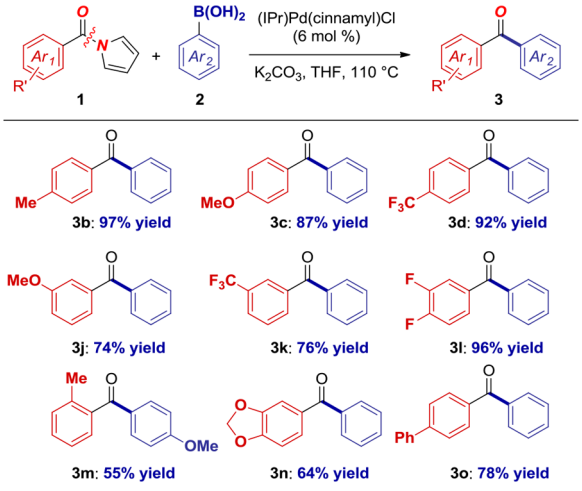


[a]Conditions: amide (1.0 equiv), Ar−B(OH)$_2$ (2.0 equiv), [Pd] (6 mol %), K_2CO_3 (3.0 equiv), THF (0.50 M), 110 °C, 15 h. [b]Isolated yields.

diverse boronic acids, including neutral (**3a**), electron-rich (**3b**−**3c**), electron-withdrawing (**3d**), sterically hindered (**3e**−**3f**), and heterocyclic boronic acids (**3g**). Cross-coupling with 4-methoxycarbonylphenyl boronic acid proceeds in unoptimized 34% yield (not shown). 4-Cyanophenylboronic acid is not tolerated. At the present stage, nitrophenyl has not been tested. Moreover, conjugated aromatic (**3h**) and challenging 2-substituted heteroaromatic boronic acids (**3i**) are well-tolerated, delivering the desired biaryl ketones in good to excellent yields.

Importantly, amides containing electron-rich (**3b**−**3c**) and -withdrawing (**3d**) substituents at the conjugating 4-position of the aromatic ring are compatible with the reaction conditions (Scheme 2). Meta-substitution with electronically diverse functional groups is well-tolerated (**3j**−**3k**). The reaction scope could be further extended to medicinally relevant F-containing (**3l**), sterically hindered (**3m**), heterocyclic (**3n**), and conjugated 4-biphenyl amides (**3o**). Interestingly, in the latter case the deamidative reduction was not observed, even though the process

Scheme 2. Amide Scope in the Pd-NHC-Catalyzed Cross-Coupling of *N*-Acylpyrroles[a]



[a]See Scheme 1 footnotes a and b.

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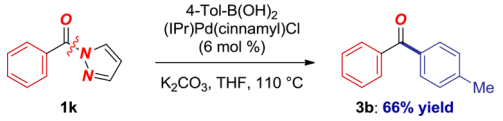
Scheme 3. Cross-Coupling of *N*-Acylpyrazole

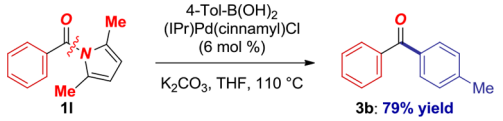


is facilitated by conjugated aromatics,[10] demonstrating the complementary scope of both reaction protocols.

We were pleased to find that the coupling of *N*-acylpyrazole proceeded uneventfully without modification of the reaction conditions (Scheme 3), despite different electronic properties of the amide bond,[16] highlighting the versatility of Pd-NHC.

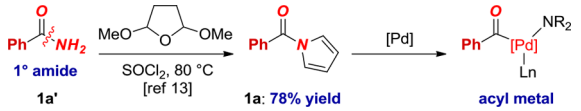
Intriguingly, the present system can be applied to couple the twisted *N*-acyl-2,5-Me$_2$-pyrrole (Scheme 4).[15] The successful coupling of sterically distorted **1l** under the same conditions as planar **1a** suggests that amide twist may not be required for N−C activation.

Scheme 4. Cross-Coupling of Twisted Amide



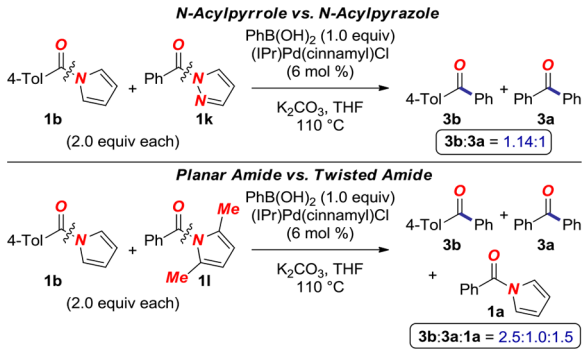
Primary amides are ubiquitous intermediates and target compounds in pharmaceutical and organic materials applications.[5,6] Since *N*-acylpyrroles can be readily prepared from primary benzamides,[13] our method offers a rapid entry to acyl-metal intermediates from unactivated primary amides (Scheme 5). Catalytic methods for direct coupling of unactivated primary amides using Pd are currently absent in the literature.[1,9n]

Scheme 5. Synthesis of *N*-Acylpyrroles from 1° Amides



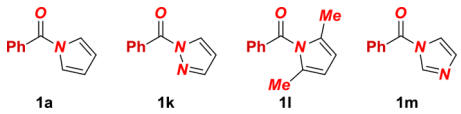
Competition studies were performed to establish the relative reactivity (Scheme 6). As shown, similar relative reactivity of **1b** and **1k** under thermodynamic conditions of the experiment was found. The intramolecular competition between planar *N*-acylpyrrole (**1b**) and twisted *N*-acyl-2,5-Me$_2$-pyrrole (**1l**) gave a mixture of products, resulting from background nucleophilic transamidation of the twisted amide bond.[17] Clearly, the use of planar amides is advantageous due to higher stability to nucleophilic capture.

Scheme 6. Competition Experiments



Kinetic studies were performed to further evaluate the relative reactivity of amides **1a**, **1k**, **1l** undergoing the coupling (Scheme 7; see Supporting Information, SI). Initial rates revealed the following order of reactivity: (**1a**) ($\nu_{initial}$ = 2.1 × 10^{-1} mM s^{-1}) ≈ (**1k**) ($\nu_{initial}$ = 2.2 × 10^{-1} mM s^{-1}) ≈ (**1l**) ($\nu_{initial}$ = 3.6 × 10^{-1} mM s^{-1}). (1) The rates parallel relative reactivity under the thermodynamic conditions. (2) All three amides react at similar rates, irrespective of electronic properties and amide twist. Collectively, the rate-determining step may not involve N−C activation under these reaction conditions. Transmetalation is generally considered as the rate-determining step in Suzuki−Miyaura couplings of aryl electrophiles.[18]

Scheme 7. Amides Employed in Kinetic and Computational Studies



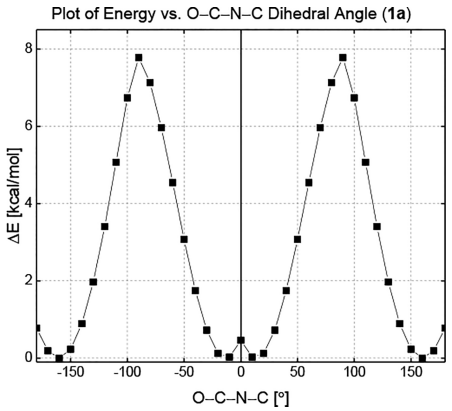


Figure 3. Rotational profile (**1a**, Δ*E*, kcal/mol, vs O−C−N−C [deg]).

Computations were employed to gain insight into the energetics of the amide bond undergoing N−C cleavage (Figure 3; see SI). *N*-Acylimidazole **1m** (Scheme 7) was included for comparison. The coupling of **1m** was unproductive under all conditions tested. It is well-established that *N*-coordination at C2/C3 in *N*-acylpyrazoles and imidazoles is facile.[16]

(1) Resonance energy (RE) determined by the COSNAR method[19] indicates that the conjugation is in the following order: **1a**, 9.3 kcal/mol; **1k**, 7.8 kcal/mol; **1l**, 2.8 kcal/mol. As expected, RE in **1a** and **1k** is much lower than in planar amides. RE in the twisted **1l** is almost completely switched off as a result of additional twist.

(2) Rotational profiles in **1a** and **1l** along the O−C−N−C$_{(Ar)}$ dihedral angle confirm amide planarity in **1a** (the energy minimum at ca. 10° O−C−N−C angle, τ = 14.44°; χ_N = 7.93°; Figure 3), and amide inverted profile in **1l** (the energy minimum at ca. 40° O−C−N−C angle, τ = 43.64°; χ_N = 4.04°; see SI).

(3) Resonance energy in *N*-ring protonated **1k** and **1m** are as follows: **1k**, 4.8 kcal/mol; **1m**, 1.0 kcal/mol (neutral **1m**, RE of 7.8 kcal/mol). As expected, *N*-coordination at the heterocyclic ring significantly weakens amidic resonance.[20]

(4) The difference between N-/O-protonation affinities (ΔPA) indicates that **1a** and **1l** strongly favor coordination

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at the amide oxygen (vs amide nitrogen, ΔPA = 21.4, 11.0 kcal/mol). However, protonation of the ring nitrogen is favored in **1k** and **1m** (ΔPA = 13.1, 26.1 kcal/mol).

Overall, the structural and energetic parameters of the amide bond combined with kinetic studies suggest that (1) N−C activation is not the rate limiting step in the coupling; (2) electronic destabilization of $n_N \rightarrow \pi^*_{C=O}$ conjugation enables selective N−C activation in *N*-acylpyrroles and pyrazoles.

In summary, we have achieved the first catalytic C−C bond formation from planar amides enabled by electronic activation of the amide N atom in *N*-acylpyrroles and pyrazoles. The method is operationally convenient and exploits *N*-acylpyrroles as Weinreb amide equivalents. These findings highlight the utility of Pd-NHC catalysis[14] in selective activation of inert amide N−C bonds. The direct synthesis of *N*-acylpyrroles from primary amides opens the door for catalytic coupling of unactivated primary amides by metal catalysis. Most importantly, the study provides an avenue for a plethora of catalytic cross-coupling reactions via acyl-metal intermediates from planar, electronically activated amides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01575.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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